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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US99/04359 <b>(22) International Filing Date:</b> 26 February 1999 (26.02.99)  <b>(71)(72) Applicants and Inventors:</b> KEEP, Marcus [US/US]; Suite 208, 2228 Lilina Street, Honolulu, HI 96817 (US). ELMER, Eskil [SE/SE]; Parternas Grande 57, S-226 47 Lund (SE).  <b>(74) Common Representative:</b> KEEP, Marcus; Suite 208, 2228 Liliha Street, Honolulu, HI 96817 (US).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> CEREBROSPINAL AND VASCULAR PHARMACEUTICAL COMPOSITION AND PROCESS FOR PREPARING THE SAME		
<b>(57) Abstract</b>  A cyclosporin-containing pharmaceutical preparation especially for cerebrospinal or vascular application is disclosed, comprising the following components: (1) at least one cyclosporin, and (2) DMSO.		

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## Cerebrospinal and vascular pharmaceutical composition and process for preparing the same.

### Description.

#### Field of the Invention:

This invention relates to pharmaceutical compositions that facilitate the administration of cyclosporins, particularly into cerebrospinal and vascular fluid spaces.

#### Background Art

##### Cyclosporin A and derivatives.

Cyclosporin A is an immunosuppressive drug. The above mentioned treatment medication has already been described, in United States Pat. No. 4,117,118 and numerous patents since, which relate to its production, formulation and immunosuppressive properties.

Cyclosporin A is a product of the fungus *Tolypocladium Inflatum* Gams. It is a cyclic poly-amino acid molecule, consisting of 11 amino acids. One of the amino acids is unique for cyclosporin A, a  $\beta$ -hydroxyamino acid called butenyl-methyl-threonine (MeBmt). The molecular weight is 1202.6 and the chemical composition is  $C_{62}H_{111}N_{11}O_{12}$ .

The molecule is highly lipophilic, and therefore virtually insoluble in water. The drug is transported in the blood within red blood cells to about 58%, and the remaining approximately 10-20% in leukocytes, and 33% bound to plasma proteins. In the plasma cyclosporin A is bound to high-density lipoprotein, low-density lipoproteins, very-low density lipoproteins and a small fraction to albumin. A very small fraction is free in plasma.

The drug undergoes extensive metabolism, mainly in the liver by the cytochrome P450 system. There are at least 30 known metabolites of cyclosporin A, with various chemical modifications, such as hydroxylation, demethylation, oxidation and epoxide formations. There are a number of variants of cyclosporin A, differing for example in one amino acid, which have similar pharmacological properties. Under normal conditions, cyclosporin A and its metabolites do not pass the blood-brain barrier. When the glycoprotein-p transporter is poisoned, or the blood-brain barrier is disrupted, cyclosporin is able to cross it and come into contact with neurons. Several analogs of cyclosporin are able to readily cross the blood-brain barrier. Several analogs of cyclosporin are not immunosuppressants. There is a subset of analogs of cyclosporin that both readily cross the blood-brain barrier and are not immunosuppressants.

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The family of cyclosporins includes cyclosporin A, cyclosporin C, cyclosporin D, and cyclosporin G. Some known metabolites of cyclosporin A include the following : (according to Hawk's Cay nomenclature) AM1, AM9, AM1c, AM4N, AM19, AM1c9, AM1c4N9, AM1A, AM1A4N, AM1Ac, AM1AL, AM11d, AM69, AM4N9, AM14N, AM14N9, AM4N69, AM99N, Dihydro-CsA, Dihydro-CsC, Dihydro-CsD, Dihydro-CsG, M17, AM1c-GLC, sulphate conjugate of cyclosporin, BH11a, BH15a, B, G, E, (and with some overlap with the Hawk's above, according to Maurer's nomenclature) M1, M2, M3, M4, M5, M6, M7, M8, M9, M10, M11, M12, M13, M14, M15, M16, M17, M18, M19, M20, M21, M22, M23, M24, M25, M26, MUNDF1 and MeBMT. Some metabolites of cyclosporin G include GM1, GM9, GM4N, GM1c, GM1c9, and GM19. Modified cyclosporins include modified C-9 amino acid analogs, modified 8-amino acid analogs, modified 6-position analogs containing MeAla or MeAbu residue, and SDZ 209-313, SDZ-205-549, SDZ-033-243, and SDZ-PSC-833.

This entire family of cyclosporins, including cyclosporin A, all derivatives, variants, amino acid variants, metabolites, including variations of mono-, di- and trihydroxylates, N-demethylates, aldehydes, carboxylates, conjugates, sulphates, glucuronides, intramolecular cyclizations and those without a cyclic structure as well as shorter peptides and amino acids and their derivatives and salts with or without immunosuppressive properties and whether able to cross the blood brain barrier or not will hereinafter be referred to as cyclosporin or cyclosporins.

Cyclosporins are highly lipophilic and virtually insoluble in water. They require an emulsifier to remain in aqueous phase, such as cremophore or Labrafil. One problem is that these emulsifiers are anaphylactic, and are neurotoxic. There is a need for an improved formulation for intravenous and oral use that is neither anaphylactic nor neurotoxic.

Further no formulation in existence is suitable for injection into the cerebrospinal fluid or the brain because of the neurotoxic and irritant properties of the emulsifiers. No formulation now exists which is used for cerebrospinal administration.

Therefore our aim was to create a unique cerebrospinal pharmaceutical composition with cyclosporin as the active ingredient that does not contain dangerous neurotoxic emulsifiers and irritants found in vascular and oral formulations.

Now we have found that if cyclosporin is dissolved in DMSO (dimethyl sulfoxide), the neurotoxic and irritant effects on the nervous system are not seen. Further we have found that not only is it a unique new cerebrospinal fluid composition with great safety and free from neurotoxicity, but that it is also an improved formulation for intravascular and oral administration too.

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## **DMSO**

Dimethyl sulfoxide is an industrial solvent derived from wood. It is biocompatible, but approved in only one condition for human use, that of interstitial cystitis, a completely unrelated bladder condition. DMSO may by itself be useful for other conditions such as scleroderma, arthritis, mental illness, and brain trauma, but is not accepted into general medical use for these conditions.

## **The Instant Invention.**

Cyclosporins are highly lipid soluble. There are well known to the art a number of mixtures for oral and intravenous administration, usually involving a carrier solution of lipid in water emulsion, micro-emulsion or nano-emulsion or particles. For intravenous administration this lipid in water emulsion is designed to allow administration in fluid phase mixed with salt-water solution to allow easy flow without precipitation of cyclosporin in the administering tubing or the blood. This has been acceptable in the past for simple intravenous (or oral) administration at the relatively low doses needed to treat immune rejection in transplantation or autoimmune disease.

It has been recently discovered that cyclosporin is neuroprotective when it comes into contact with neurons. Since the drugs are also systemically immunosuppressive, it would be desirable to administer them selectively into the brain or the cerebrospinal fluid around the brain. Nonsystemic local CSF administration of cyclosporin would reduce systemic immune suppression, and increase brain and spine neuron exposure compared to systemic administration, both very desirable goals in patients in need of neuroprotection but not in need of immunosuppression. Especially patients that need long term treatment neuroprotection (such as those with amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease), it is desirable to avoid the complication, or undesirable side effect of lifelong systemic immunosuppression.

Lipids emulsifiers are used in Sandimmune (Novartis' formulation for cyclosporin) such as a modified castor oil derivative (Labrafil and cremophore). These castor oil derivatives have been themselves found to be directly neurotoxic, and likely to be the cause of the reported cases of neurologic problems of encephalopathy, and seizures in transplant patients.

Other formulations use less neurotoxic lipid formulations such as tocopherols. However lipids injected into the cerebrospinal fluid have been reported to cause severe complications of arachnoiditis or inflammation around the spinal cord-such as the discontinued oil based Pantopaque intrathecal X-ray contrast used in spinal myelograms. Injecting lipids, even in micro or nano-emulsions into the cerebrospinal spaces would likely cause layering of the lipid, since the long column of fluid in the spine contains slow moving CSF, which is a very different milieu than the rapidly

flowing and mixing turbulent arterial and venous blood. The layering of lipid and drug in the cerebrospinal fluid column would result in undesirable cyclosporin over or underdosage, depending on location.

In addition, ethanol is a commonly used solvent for cyclosporin used in Sandimmune and SangCya (Sangstat's cyclosporin formulation). Ethanol is a known neurotoxin, and is used for neurolysis or destruction of nerve roots by injection into the brain or cerebrospinal fluid spaces.

It is now found to be desirable to inject cyclosporin into the fluid contained within the brain, and in which the brain floats, the cerebrospinal fluid. Clearly all previously described oral preparations, and all previously described intravenous preparations are not suitable because they contain neurotoxins and irritants as solvents or emulsifiers. In addition the known intravenous formulations are not ideal for intravenous use because they contain neurotoxins which causes the documented manifestations of neurotoxicity in patients obtaining intravenous or oral administration. Cerebrospinal injections of these intravenous formulations would cause unacceptable and potentially lethal neurotoxic effects.

All previous formulations for cyclosporin have utilized a lipid emulsifier to obtain solubility. It would not be expected by a person skilled in the art that a completely different class of compound other than a lipid emulsifier, such as the industrial solvent DMSO would turn out to be suitable for intracerebrospinal administration. Further they would not expect that the use of an industrial solvent would be an improvement over existing intravascular and oral cyclosporin compositions.

This novel formulation for administering cyclosporin into the CSF is the use of dimethylsulfoxide (DMSO) as the carrier medium or solvent. Cyclosporin is very soluble in DMSO. Unlike castor oil derivatives or ethanol, DMSO is not neurotoxic. It is highly biocompatible and is actually a known neuroprotectant in its own right. It is possible to safely administer DMSO. DMSO prevents precipitation of cyclosporin even when diluted in the CSF.

In addition DMSO easily crosses tissues barriers in its role as a solvent and carries in with it drugs dissolved in it. This is an advantage because it opens the blood-brain barrier and CSF-brain barrier to facilitate cyclosporin penetration into the brain.

The two main methods for infusing the formulation will be via the cerebral ventricles and the thecal sac. A catheter placed through a scalp incision, a skull twist drill hole and the brain, will access the cerebral ventricles. If a short-term infusion of several days is desired the catheter would be remain externalized and then removed. If a long term infusion over months or years were desired, the skin would be closed over the catheter and an attached refillable reservoir or drug pump.

Thecal sac infusion is typically by lumbar puncture in the lumbar spine (or less often at the top of the spine at the base of the skull). The spinal puncture needle is placed through the skin of the back and pierces the dura (thecal sac) which contains the CSF in which the spinal cord is floating. Once in, formulary drug can be infused into the CSF in one session via the needle, or over a week through a soft catheter. For long term infusion over months or years, the soft catheter is connected under the skin to a refillable programmable pump that is usually implanted under the abdominal skin.

In addition to being a novel, unique, efficacious and safe formulation for intrathecal administration, this formulation is also superior for intravenous or intra-arterial administration. The absence of systemic neurotoxic castor oil derivatives will reduce the well-known neurological complications. The tissue penetrating capabilities of DMSO will facilitate penetration of the blood-brain barrier by cyclosporin to come into contact with neurons to make it work better.

#### **Medicament and administration.**

The formulary drug can be administration by the routes including oral, sublingual, buccal, nasal, inhalation, parenteral (including intraperitoneal, intraorgan, subcutaneous, intradermal, intramuscular, intra-articular, venous (central, hepatic or peripheral), lymphatic, cardiac, arterial, including selective or superselective cerebral arterial approach, retrograde perfusion through cerebral venous system, via catheter into the brain parenchyma or ventricles), direct exposure or under pressure onto or through the brain or spinal tissue, or any of the cerebrospinal fluid ventricles, injections into the subarachnoid, brain cisternal, subdural or epidural spaces, via brain cisterns or lumbar puncture, intra and peri-ocular instillation including application by injection around the eye, within the eyeball, its structures and layers, as well as via enteral, bowel, rectal, vaginal, urethral or bladder cisternal. Also for *in utero* and perinatal indications then injections into the maternal vasculature, or through or into maternal organs including the uterus, cervix and vagina, and into embryo, fetus, neonate and allied tissues and spaces such as the amniotic sac, the umbilical cord, the umbilical artery or veins and the placenta, with parenteral being the preferred route.

The formulary drug, containing cyclosporin dissolved in DMSO, for administration into the brain and related structures, spinal cord and related structures, ventricular system and cerebrospinal fluid spaces can be manufactured and distributed containing, aqueous and non-aqueous injection solutions, other pharmaceutically active compounds, additives including anti-oxidants, bacteriostats and solutes and sugars such as mannitol to make the formulary drug isotonic, hypotonic or hypertonic with the cerebrospinal fluid; and also aqueous and non-aqueous sterile suspensions. The formulary drug can be manufactured and distributed in unit-dose or multi-dose containers, such as sealed glass or plastic ampoules, vials, bottles and bags as a liquid, and in a dry state requiring the addition of DMSO.

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The formulary drug for parenteral administration can be manufactured from cyclosporin, DMSO, aqueous sterile injection solutions, other pharmaceutically active compounds, additives including anti-oxidants, bacteriostats and solutes and sugars such as mannitol to make the formulary drug isotonic, hypotonic or hypertonic with the fluids of the recipient. The formulary drug can be manufactured and distributed in unit-dose or multi-dose containers, such as sealed glass or plastic ampoules, vials, bottles and bags as a liquid, and in a dry state requiring the addition of DMSO.

The formulations are used in patients who require neuroprotection from neurological diseases of acute to chronic nature including stroke, brain hemorrhage, brain and spine trauma, ionizing radiation, neurotoxicity to vestibulocochlear structures, retinal detachment and neurodegeneration including amyotrophic lateral sclerosis, Parkinson's and Alzheimer's.

The formulations are used in patients who require both neuroprotection from neurological disease and that their neuro-axis be immunocompromised, such as in neural transplantation, neural xenotransplantation, multiple sclerosis, HIV neuropathy and Guillain-Barré syndrome.

The formulations are used in patients who require that they be immunocompromised, such as in transplantation and autoimmune disease.

The formulations are used for topical application for patients who require immunocompromise of the skin for diseases such as psoriasis.

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The formulary drug generally contains from 0.1 to 90% of the treatment medication by weight of the total composition. Cerebrospinal doses between 5 mg and 5 gram per day are possible, with about 50-150 mg/day for chronic administration, and 100-1000 mg/day for acute administration being preferable. Amounts of from 0.0001 mg to 200 mg/kg, or preferably 0.001 to 50 mg/kg, of body weight per day for parenteral administration and 0.001 to 150 mg/kg orally, can be given. Nevertheless, it could be necessary to alter those dosage rates, depending on the condition, weight, and individual reaction of the subject to the treatment, and the mode in which the administration is carried out, and the stage of the disease process or interval of administration. It may thus be sometimes adequate to use less than the before stated minimum dose, while in other instances the upper limit must be surpassed to obtain therapeutic results.



**Examples:****Example 1**

Sterile Injectable Concentrate Formulary Drug with cyclosporin as active ingredient

Containing per ml:

Cyclosporin A	200	mg
DMSO	800	mg

The formulary drug is made by dissolving 5 grams of cyclosporin into 20 grams dimethyl sulfoxide at room temperature. The solution thus obtained is made up to 25 ml with water. The solution is homogenized with stirring and filtered. The liquid is sterilized by radiation and then placed in a sealed container such as glass under inert gas atmosphere in doses of 1, 5 or 25 ml.

Sterile injectable concentrate formulary drug is administered, with or without dilution with for example isotonic saline, by infusion or by injection into cerebrospinal fluid spaces, brain, spine, vein or artery.

**Example 2**

A person in need of acute brain or spinal neuroprotection from trauma or stroke has the composition of example 1 injected into the cerebrospinal fluid of the ventricle of the brain through a burrhole in the skull, or into the cerebrospinal fluid of thecal sac via a lumbar puncture needle, or injected intravascularly.

**Example 3**

A person in need of chronic brain or spinal neuroprotection from neurodegenerative disease such as Parkinson's, Alzheimer's or amyotrophic lateral sclerosis has the composition of example 1 injected periodically by a reservoir or pump into the cerebrospinal fluid of a brain ventricle through a burrhole in the skull, or into the cerebrospinal fluid of the thecal sac via a lumbar catheter connected to a reservoir and pump.

**Example 4**

A person in need of neural immunosuppression for neural transplantation, neural xenotransplantation, or diseases with autoimmune components like multiple sclerosis, Guillain-Barré, has the composition of example 1 injected periodically by a reservoir or pump into the cerebrospinal fluid of a ventricle of the brain through a burrhole in the skull, or into the cerebrospinal fluid of the spinal thecal sac via a lumbar catheter connected to a reservoir and pump.

**Example 5**

A person in need of systemic immunosuppression has intravenous injections or oral consumption of the compositions of examples 1.

**Industrial Applicability**

From the above description it will be evident that the present invention provides improved compositions for the administration of cyclosporin. Additionally the present invention provides a completely new composition suitable for administration directly into the new target of delivery, the cerebrospinal fluid to directly treat diseases of the brain, which previously described compositions are not suitable for, because of the neurotoxicity of their solvents.

No precipitation was observed with an initial one month of testing of composition prepared according to example 1. Ampoules stored in darkness containing 5 ml stored at 0, 30, and 60 degrees C show neither discoloration nor precipitation.

Rats receiving intraventricular cerebrospinal infusions showed no neurotoxicity, seizures or untoward effects. In addition, rats receiving injections intravenously showed no ill effects.

**Claims:** What is claimed is:

1. A pharmaceutical composition of matter in the form of a solution concentrate comprising a cyclosporin dissolved in DMSO.
2. A composition as in claims 1 wherein the cyclosporin is cyclosporin A.
3. A method for administering cyclosporin into cerebrospinal fluid spaces, including intraventricular and intrathecal, in a patient, the improvement which comprises: providing cyclosporin dissolved in DMSO in a pharmaceutically acceptable carrier, and administering said cyclosporin and DMSO solution by injection into the cerebrospinal fluid spaces to said patient.
4. A method for administering cyclosporin by injection including intra-ocular, intravestibular, into or adjacent to the brain, or spinal cord into a patient, the improvement which comprises: providing cyclosporin dissolved in DMSO in a pharmaceutically acceptable carrier, and administering said cyclosporin and DMSO solution by injection intra-ocular, intravestibular, into or adjacent to the brain, or spinal cord to said patient.
5. A method for administering cyclosporin by injection including intravenous, intra-arterial or intraparenchymal, into a patient, the improvement which comprises: providing cyclosporin dissolved in DMSO in a pharmaceutically acceptable carrier, and administering said cyclosporin and DMSO solution by injection into intravenous, intra-arterial or intraparenchymal spaces to said patient.
6. A method for administering cyclosporin orally, rectally, nasally or dermally to a patient, the improvement which comprises: providing the cyclosporin dissolved in DMSO in a pharmaceutically acceptable carrier, and administering said cyclosporin and DMSO solution orally, rectally, nasally or dermally to said patient.
7. The method of claims 3,4,5, and 6 wherein the cyclosporin is cyclosporin A, or functional derivatives, metabolites, variants or salts thereof.
8. An article of manufacture comprising packaging material and pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for reducing or preventing neuronal damage and for causing immunosuppression when administered in a therapeutically effective quantity, and wherein the packaging material comprises a label which indicates that the pharmaceutical agent can be used for reducing or preventing neuronal damage and for causing immunosuppression, and wherein said pharmaceutical agent comprises DMSO and a cyclosporin such as cyclosporin A or a compound of the class of cyclosporins, or functional derivatives, metabolites, variants or salts of them thereof, or combination of the before said, either alone or in admixture with diluents, or additives

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/04359

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :A61K 38/00

US CL :514/11

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/11

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPATFULL, HCAPLUS, MEDLINE- cyclosporins in compositions together with dmso.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,827,834 A (FALK et al.) 27 October 1998, columns 3 and 10.	1-6 and 8
Y	US 5,811,410 A (FALK et al.) 22 September 1999, columns 11 and 17.	1-6 and 8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

26 APRIL 1999

Date of mailing of the international search report

14 MAY 1999

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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/04359

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☒ Claims Nos.: 7  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.